Report 4 of the Research Committee for International Pharmaceutical Distribution of the Federation of Japan Pharmaceutical Wholesalers Association

International Comparison of the Drug Pricing Systems and Distribution of Generic Pharmaceuticals

December 2017

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1. Purpose of This Report

Generic drug distribution volumes in the Japanese pharmaceuticals market have increased dramatically in recent years due to several factors, including the *Basic Policy on Economic and Fiscal Management and Reform 2015* established in June 2015 (the so-called "Honebuto Policy") which set the goal of achieving 80% generic drug use on a quantitative basis and an increase in the patent expirations of major drugs. Japanese pharmaceutical wholesalers are facing financial pressure mainly due to two factors: 1) decreased sales and profit caused by substitutions of patent-expired products with low-priced generic drugs, and 2) increasing storage costs of various types of generic drugs. Pharmaceutical wholesalers are being forced to improve the productivity of their handling of these drugs.

The Proposal regarding the Improvement of Commercial Transaction Practices of Ethical Drugs, issued on September 1, 2015, emphasized that a stable supply is the premise for promoting the further use of generic drugs, noting that "at the very least, measures must be taken to avoid confusion in commercial distribution practices by the middle of FY2017." *The Overall Strategy for Strengthening the Pharmaceutical Industry*, published September 4, 2015, suggested that acceleration in the use of generic drugs must be accompanied by an examination of institutional and legal systems—such as generic drug pricing brackets and the approaches to marketing—along with the stabilization of distribution.

The Research Committee for International Pharmaceutical Distribution conducted a study to obtain suggestions regarding the stable supply of future Japanese generic drugs and productivity improvements in the distribution of generics drugs. Four Western countries where progress is being made in the use of generic drugs (France, Germany, the United Kingdom, and the United States) were chosen so as to examine their systems and distribution situations. The future handling of generics drugs in Japan was then proposed.

The survey was conducted by sending questionnaires to on-site individuals at pharmaceutical companies in Japan and wholesalers in Western countries, and using public materials, such as articles and websites. The questionnaires and hearings were conducted from September 2016 to April 2017, and the articles and websites examined were those available publicly as of 2016.

2. Definition of Terms

This report uses the terms related to pharmaceuticals as follows:

- Patented product: A medical pharmaceutical that is still within the exclusive sales period (patent period and re-examination period).
- Patent-expired product: A medical pharmaceutical whose exclusive sales period (patent period and reexamination period) has ended.
- Generic: Medical pharmaceuticals that are marketed with approval from the relevant authorities after the monopolistic sales period (patent period and re-examination period) on a patented product has ended.

In this report, the term "generic" has the same meaning as the term "generic drug" used in Japanese government notifications. To avoid confusion in the interpretation of terms in the international comparison, the definition of "generics" above shall be used throughout this report. However, when citing an administrative notice or other such document, the original text of the notice shall be used.

An "authorized generic" (AG; see footnote) refers to a drug that is marketed after the relevant licensing is obtained, such as patent rights, from the company that markets the patented product (original drug). An AG is commercially available as a generic drug before the exclusive sales period has ended and is considered to be a "generic" in this report.

The name of the pharmaceutical product is written on the script, and the naming of generics will have substantial impact on how generics are marketed; therefore, this report classifies generics into three categories based on the name of the generic on the label: INN generic, INN generic with the company name, and generic with its own unique name.

- INN generic: A generic with an International Nonproprietary Name (INN).

Examples

UK: Pravastatin Sodium 10mg Tablets

US: Pravastatin Sodium Tablets USP 10mg

- INN generic with the company name: INN and the company name (or a symbol reflecting that company).

Examples

France: Pravastatin TEVA 10mg comprimé

Germany: Pravastatin AL 10mg

Japan: Pravastatin Na Tab. 10 mg "TEVA," Pravastatin Na 10 mg "EE"

- Labeled generic (generics with their own unique name): A generic named after a product name different from the patented product name or INN.

There are cases in which a unique name is used to differentiate products or where a unique name has been used prior to the change of the labeling policy.

Examples

UK: Adizem-SR (patented product Tildiem-LA, generic name Diltiazem) – Differentiation purposes

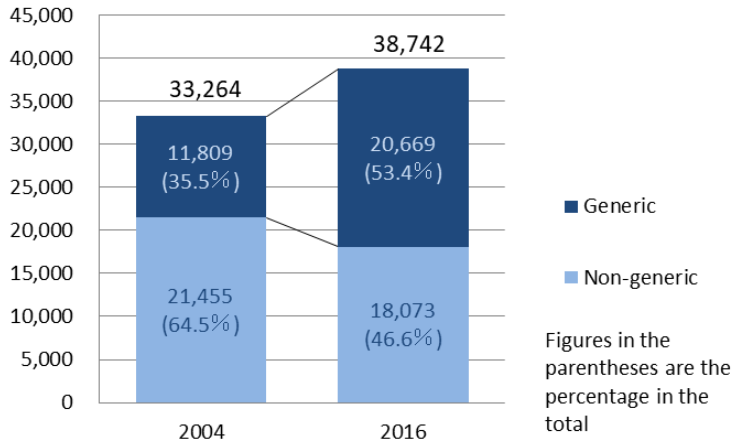
Japan: Alsetin 10 (patented product Mevalotin, generic name Pravastatin) – Continuation of the old name

Note: In the United States, if a company submit the first generic application and if that is approved, monopolistic sales are permitted for 180 days. To combat against these monopolistic sales, the manufacturers and sellers of patented products sell their products as AGs through the sales channels outside of their own companies.

3. Number of Packaging Types Handled by Pharmaceutical Wholesalers

Despite measures to promote generic use and to stipulate quantitative targets, an increase in the number of pharmaceutical companies and packaging types has placed significant burden on pharmaceutical distributors. The total number of packaging types handled by pharmaceutical wholesalers (in March of any given fiscal year) increased 1.16-fold from 33,264 in fiscal 2004 (prior to the introduction of quantitative targets) to 38,742 in fiscal 2016—the most recent year. During that same period, the number of packaging types of generics rose 1.75-fold from 11,809 to 20,669. The percentage of generics in the total number of package types grew 17.9 % from 35.5% in fiscal 2004 to 53.4% in fiscal 2016 (Figure 1).

Figure 1: Trends in the Number of Packaging Types Handled by Pharmaceutical Wholesalers



Source: CRECON R&C

Even from a global perspective, the number of packaging types in Japan is substantial.

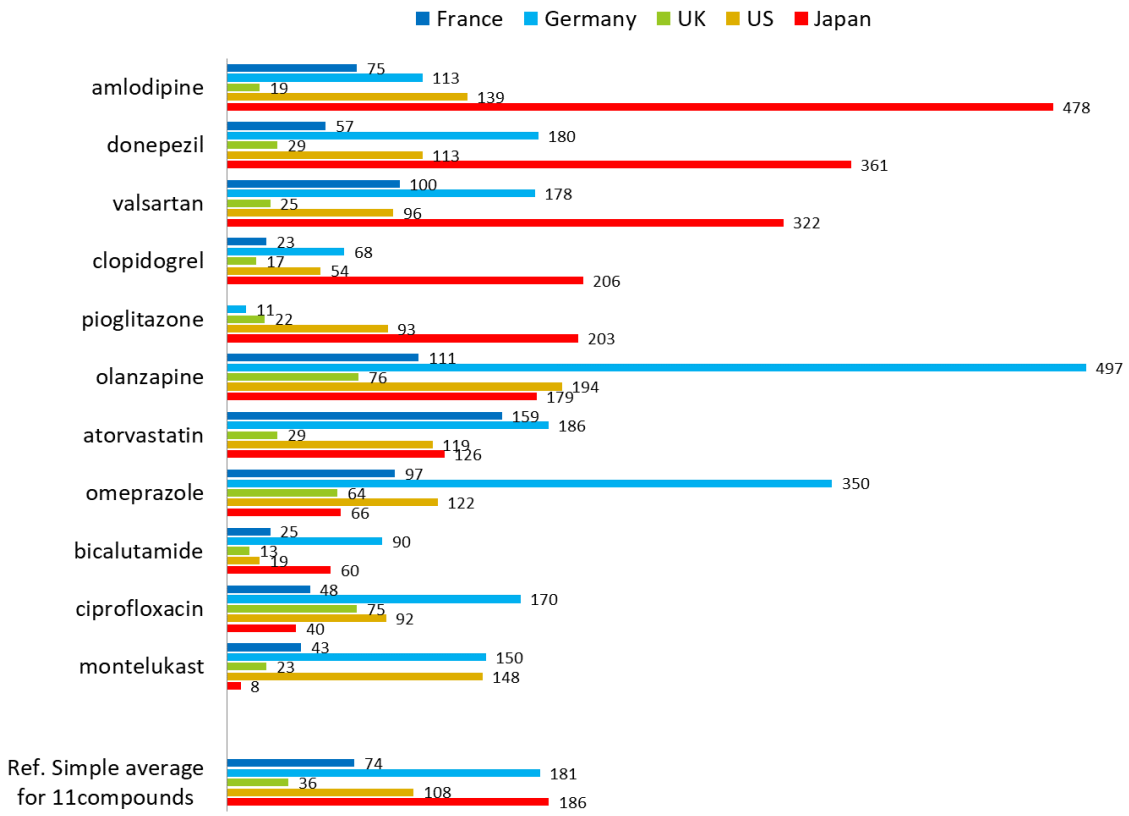
Figure 2 shows the results of a survey of the number of packaging types sold for each representative drug in different national markets for 11 widely used therapeutic categories (vasodilator, Alzheimer's therapeutic, hypotensive agent, antiplatelet drug, type-2 diabetes drug, antipsychotic, hyperlipidemia agent, peptic ulcer medication, prostate cancer drug, antibiotic, and asthma drug). The categories are sorted in descending order with the number of different packaging types available in Japan. The data for a single year was collected up to September 2016, and patent-expired products are included.

Figure 2 confirms that the number of packaging types varies widely among countries, and many packaging types for each compound are available in Japan and Germany followed by the United States and France. The United Kingdom has relatively few types. It can be argued that the large numbers of availability of packaging types in Japan are due to an increase in joint development among pharmaceutical companies.

Table 1 provides the number of generic pharmaceutical companies in each country, based on membership in generic

drug associations. Of the five countries, Japan and Germany have the most generic pharmaceutical companies, followed by the United Kingdom. Therefore, the number of generic pharmaceutical companies alone does not explain the reason for the number of available packaging types.

Figure 2: Number of Packaging Types Sold in Each Country (for the sales period October 2015 to September 2016)



Source: IMS

Table 1: Number of Generic Manufacturers in Each Country

France	・ There are 21 companies (including biosimilar drug manufacturers) that are members of the French generics association GEMME.
Germany	・ There are 15 companies (including biosimilar manufacturers) that are members of the German generics association Progenerika, accounting for 77% of the market (on a volume basis). ・ There is a total of 80 companies. ・ Smaller generics manufacturers are either under the control of larger generic companies or under an OEM production contract and are not independent. As in Japan, many generics become available at once when a patent of the drugs expires. There is no rule to prepare all package types for approval.
UK	・ There are 30 companies (including biosimilar manufacturers) under the British generics association BGMA, accounting for about 90% of the market (on a volume basis). ・ There is a total of 70 companies, including small and medium-sized operations.
US	・ There are 31 companies (including biosimilar manufacturers) that are members of the US generics association, GPhA.
Japan	・ Of the generics companies that market generics in the NHI drug list as of February 2017, 38 are members of the Japan Generic Medicines Association, and 41 are members of the Japan Pharmaceutical Manufacturers Association.

Source: The websites for the various national generics associations; the Institute for Health Economics and Policy; and the Mizuho Information & Research Institute, Inc.

4. Comparison of Generics Pricing Systems

It is essential to understand the generic drug price systems in these countries with a wide penetration of generic drugs, in order to gain insights from surveys of generic distribution practices. This section focuses on product names and reimbursement pricing for which international comparisons are possible. For the United Kingdom, the drug pricing systems for England and Wales were analyzed. This section uses the essences of the drug price systems to compare the systems among the countries in question.

A) Generic Product Names

In France, Germany, and Japan, generics are typically INN generics with the company name, whereas in the United Kingdom and the United States, INN generics are used. There are also labeled generics in each country. In France, Germany, and Japan, these are handled just like other generics and can be substituted when necessary. In the United Kingdom and the United States, labeled generics cannot be substituted.

1) France

INN generics with the company name (some are labeled generics)

2) Germany

INN generics with the company name (some are labeled generics)

3) UK

INN generics (some are labeled generics)

4) US

INN generics (some are labeled generics)

5) Japan

INN generics with the company name (some are labeled generics)

B) Reimbursement Pricing for Generics: Determination and Variability

Here we consider two aspects of the system for reimbursement pricing in each country:

- Methods of determining reimbursement prices for generics
- Whether there is variability in reimbursement pricing for generics (for identical compounds, identical dosage forms, identical specifications, and identical number of products [henceforth referred to as identical packaging])

1) France

- Method of Determining Reimbursement Prices for Generics[1]

The reimbursement price is the pharmacy sales price, which is calculated for each packaging type as follows:

> [40% of the net manufacturer shipping price of the patented product + official wholesaler margin + official pharmacy margin + value-added tax]

After 18 months, this price is discounted by 7%, and after that the Economic Committee of Health Care Products

(CEPS) can decide to re-adjust the price based on such factors as price differences in the same medicinal group and market impact.

- Variability in Reimbursement Prices for Generics

There is no variation in pricing because the reimbursement price for generics with identical packaging is calculated based on the above formula and on the net manufacturer shipping price of the identical patented product. There is also no variation in any subsequent revised pricing. (See Figure 3. For an explanation of France's reference price system [TFR] mentioned in the figure, see Explanation 1.)

2) Germany

- Method of Determining Reimbursement Prices for Generics[2]

The reimbursement price basically is the pharmacy sales price, which is calculated for each packaging type as follows:

[Net manufacturer shipping price + official wholesaler margin + official pharmacy margin + tax]

The net manufacturer shipping price is set freely by the pharmaceutical company. However, for generics, a reference price is set when around three generics have come to market after the patent for the drug has expired, and the reimbursement price for the generics cannot exceed this reference price. As a general rule, this reference price is adjusted once a year.

- Variability in Reimbursement Prices for Generics

While there are some cases where the pharmacy sales prices for generics in identical packaging will match the reference price, it is more typically the case that there will be choices that are priced below the reference price (Figure 4). This is because pharmaceutical companies have incentives to lower their prices. For example, the co-payment will be relieved if the pharmacy sales price is 30% or more below the reference price. There are also discount contracts with the so-called "sickness funds." Therefore, there is no uniformity in reimbursement prices.

Fig. 3 Example of the pharmacy sales price in France

Fig. 3-1 TFR-applied case (bicalutamide: partial)

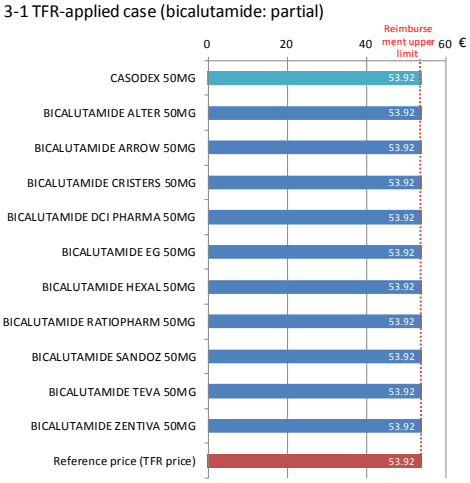


Fig. 3-2 TFR non-applied case (glimepiride: partial)

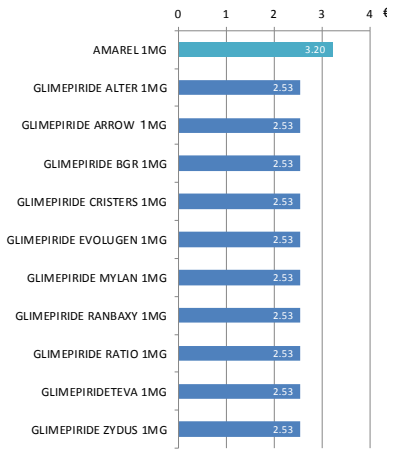
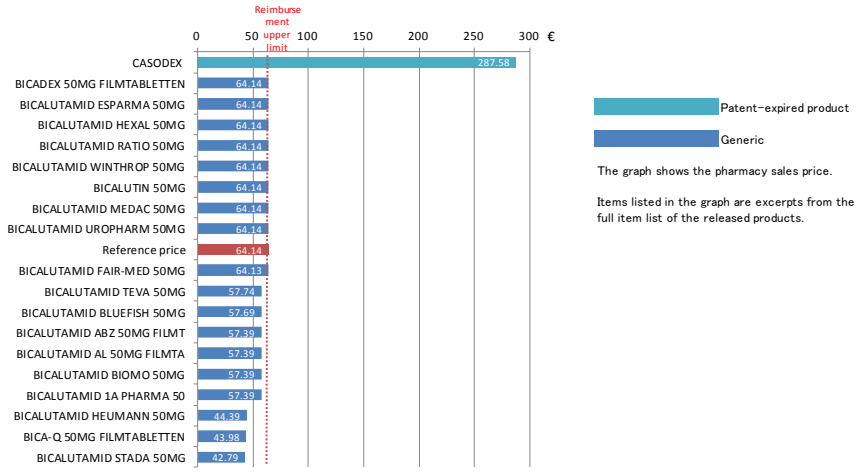


Fig. 4 Example of the pharmacy sales price in Germany (bicalutamide: partial)



(Source: Drug price lists of each country)

3) UK

- Method of Determining Reimbursement Prices for Generics[3]

For INN generics, pharmaceutical companies are free to set prices based on Scheme M (see Explanation 2) as negotiated by the Department of Health and the British Generic Manufacturers Association, and those prices are used as the reimbursement prices. This rule applies to generics that fall under Drug Tariff Category M (see Explanation 2). The Department of Health adjusts the reimbursement prices every three months based on customer purchase prices so that pharmacy gross margins on sales (the difference between the reimbursement price and the purchase price) are a certain amount. Labeled generics do not fall under Scheme M, and the pharmaceutical companies set the sales prices. The reimbursement price includes the wholesaler margin and the pharmacy margin.

- Variability in Reimbursement Prices for Generics

For drugs prescribed for outpatients, the Drug Tariff sets and lists one reimbursement price for every dosage form, specification, and contained volume of each medicinal compound. In other words, there is generally no variation in reimbursement prices for generics (see Footnote 1 for the exceptions).

4) US

- Method of Determining Reimbursement Prices for Generics[4]

Pharmaceutical companies set the wholesale acquisition price (WAC; see Footnote 2) based on patented products prices. The private insurance reimbursement price is determined by the discount rate that has been negotiated between the pharmaceutical company and the insurer based on the WAC and the average wholesale price (AWP; see Footnote 3) that is calculated based on the WAC. For public insurance such as Medicaid, the reimbursement prices are determined based on negotiations between the drug manufacturers and the state governments. Medicare Part D (the prescription drug benefit plan) is a federal government program, but the reimbursement prices are set by the private insurance companies because operations and the actual drug benefits are managed by private insurance companies.

- Variability in Reimbursement Prices for Generics

There is variability because the WACs are determined by the pharmaceutical companies and the reimbursement prices are determined through negotiation.

5) Japan

- Methods of Determining Reimbursement Prices for Generics

When a generic is added to the National Health Insurance drug list, it is priced at 50% of the patented drug (or 40% for oral medicines if more than 10 are added at the same time), and then adjusted once every two years based on customer purchase prices. Prices are set for each medical compound, dosage form, and specification, but not for each packaging type.

- Variability in Reimbursement Prices for Generics

For generics, the prices for identical compounds, identical dosage forms, and identical specifications are grouped in a maximum of three price brackets. As of the price revisions made in fiscal 2016, 80% of generics were priced in a single price bracket.

Note 1: In the United Kingdom, INN name prescriptions are generally used, but if a prescription uses the product name, that product must be dispensed (see Explanation 3). The Drug Tariff specifies the reimbursement prices when INN is prescribed. Reimbursement prices when a labeled generic is prescribed as a product name may not be listed in the Drug Tariff. That is, if a labeled generic exists, there may not be uniform reimbursement price even for identical packaging.

Note 2: Wholesale Acquisition Cost (WAC): The prices charged by pharmaceutical companies in the United States to wholesalers. These do not include discounts or rebates. These are set and published by the pharmaceutical companies.

Note 3: Average Wholesale Price (AWP): Not a legal definition, but these are the prices referred to by ordinary insurers for reimbursements applied to drug benefits. A markup is calculated and applied to the WAC (generally 1.2 or 1.25). These are published by price setting service agencies, such as publishers.

5. Conditions regarding Stable Supply of Generics in Multiple Countries

This section summarizes the supply stability of generics in each country, based on hearings with pharmaceutical wholesalers in the United States and Europe and two reports by the Economic Affairs Division of the Health Policy Bureau of Japan's Ministry of Health, Labor and Welfare (a fiscal 2013 report on the industrial promotion of generics and measures to ensure their availability and a fiscal 2015 research report on drug usage).

1) France[5]

Pharmacists can decide to dispense a substitute (see Explanation 3).[6] The supply shortages of generics are not an issue at pharmacies. Generics can be substituted for patent-expired products, so shortage of any individual generic is seldom an issue.

- Pharmacies do not experience the problem of drugs being out of stock. Even if a particular company's product may run out of stock, pharmacies dispenses generics from other pharmaceutical companies' generics as a substitute; They ordinarily uses two or three pharmaceutical companies for the identical packaging of generics.
- As is the case in other countries, both patented drugs and generics can become out of stock when the active pharmaceutical ingredient is not available.

2) Germany[7]

In some regions, shortages are becoming a serious issue. As described below, this may be partially due to the system of discount contracts (see Explanation 3) and the excessive bidding that has lowered prices.

The advantages of discount contracts:[8]

- Reduces the costs of medicines (The sickness funds saved roughly 3.15 billion euros in 2014 through this system.)
- Reduces the co-payment (When drugs that are subject to discount contrasts are dispensed, the co-payment can be reduced or eliminated.)

The disadvantages of discount contracts:

- Concentration of pharmaceutical companies; when a company withdraws from a market, the remaining companies may not pick up the slack; thus, shortages can occur. There is a significant concentration of companies in the market for antibiotics. If this trend continues, it will become difficult to ensure stable supplies. The sickness funds are contracting with three pharmaceutical companies instead of just one company.
- Pharmaceutical companies are unable to predict the actual required supply volumes. Production plans for generics are typically launched six months in advance, so sudden increases in demand often cannot be accommodated.
- Contracts are bid, and this can lower prices so far that pharmaceutical companies cannot cover a rise in material costs and labor costs.
- Pharmaceutical companies that cannot supply the drugs during the contract period are penalized with

fines.[8]

- Pharmacies must dispense different generics to different patients depending on which sickness funds they are in, and even with search software this places a burden on pharmacy operations.[9] There are 118 different sickness funds nationwide (as of March 2016).[10]

3) UK[11]

The supply stability situation differs for the pharmacy and hospital markets.

Pharmacy Market

- Several pharmaceutical companies participate in the pharmacy market. If one company cannot supply a product, other companies will; neither drugs do go out of stock nor are in a short supply (some 92% of all orders placed to wholesalers are delivered within 24 hours).
- Inventories in pharmacies are managed using INN. When the pharmaceutical wholesaler does not have the product of a regularly used pharmaceutical company in stock, they can deliver identical products from their inventory. As a result, pharmacies will sometimes purchase the product of another drug manufacturer.[12]
- An excessive decline in the reimbursement price can make the purchase price higher than the reimbursement price. When this happens, the pharmacy files a report online, and steps to temporarily (for one month only) increase the reimbursement price are taken.[13]

Hospital Market:

- Hospitals use a bidding system and decide on the number of suppliers and the supply volume with each supplier. Therefore, if a company cannot supply its volume, other companies may not make up the difference. As a result, supply shortages actually occur for the products of the contracted companies.
- If a contracted pharmaceutical company cannot procure the agreed-to product, the hospital will procure a substitute (patent-expired product or generic), and a penalty will be charged to the company to cover the difference in price. Pharmaceutical companies strive to provide stable supplies to avoid such damage.

4) US[14]

An increase in the number of cases of drug shortage has been observed, from 40 in 2007, 261 in 2012, and 288 cases in 2013. Most cases involved a shortage of generic injectables. These are typically manufactured by one or two companies and by four companies at most. Even if only one company runs out of its stock, a market-wide drug shortage can occur.

- Most drug shortages are due to quality issues (e.g., contamination with microbes, or with glass or metal particles) and production delays, and problems with supply capacity. A decrease in supply capacity can result from a response to quality issues like a change in GMP standards. Underlying this is limited equipment investments and withdrawals from the market due to low profitability (narrow margins).

- The steep rise in the prices of generics in recent years has become a social issue due to multiple factors, including drug shortages, concentration of the market via mergers, and shortages of active pharmaceutical ingredients.

Highlights

UK: Communications from the National Health Service (NHS) on Labeled Generics[15]

The NHS has issued the following warning regarding brand prescribing and the use of labeled generics at pharmacies (excluding cases in which the physician deems their adaptation to be necessary because of a formulation change or device improvement).

- The NHS coordinates things so that the gross profit of pharmacies in Category M is £800 million. The use of INN generics contained in Category M is most cost effective for the NHS.
- The pharmaceutical companies of labeled generics may lower the prices of their own products below Category M, but prescriptions of labeled generics ultimately end up increasing NHS costs because they prevent price competition among generics.
- When using labeled generics, it is important to adequately take into account such factors as price fluctuations, supply volumes, reliable access to distribution channels, and the provision of information on safety and other matters.

US: Rising Prices for Generics

The rising price of generics has become a major social problem in the United States. A study conducted by the US Senate revealed that the prices of 10 types of generics rose at the minimum 388% and at the maximum 8,281% from October 2013 to April 2014.[16] Also, after the generic version of the anti-infective agent Daraprim, for AIDS patients began to be sold exclusively by Turing, the price rose from USD 13.50 to USD 750 in just two months starting in August 2015. This was a major social problem.[17] There is no law preventing generic pharmaceutical companies from raising their prices through monopolistic manufacturing.[18] However, this is not just a problem for exclusive manufacturing. When a drug is produced by eight companies and one company raises its prices, the others sometimes follow suit.[19]

Table 2 summarizes the discussion in this section about the supply stability of generics, the aspects related to supply stability in the discussion in section 4 about the pricing systems for generics, and indicators of the market penetration of generics in each country.

Table 2. Country-Specific Comparison of the Supply Stability of Generics and Drug Pricing Systems

	France	Germany	UK	US	Japan
Conditions regarding Stable Supply of Generics†					
Manufacturing problems	—	Bidding for discount contracts by the sickness funds has led to a concentration of pharmaceutical companies and the occurrence of stockouts	Stockouts due to the bidding system (in the hospital market)	Many instances of stockouts, due to the concentration of pharmaceutical companies and withdrawals from market due to thin margins	—
Price	—	—	Excessive decline in reimbursement prices creates situations where products	Some products become very expensive	—

				cannot be purchased at those prices (in the pharmacy market)		
Pharmacy inventories		Stockouts are not seen as a problem because products are handled from two to three companies	Each sickness fund uses different items, increasing the burden on inventories	Drugs are managed by INN, and business is done with multiple companies, so stockouts do not occur	—	Excessive number of different kinds of packaging increases the burden on inventories
Generic Price Systems						
Representative generic product names		Yes	Yes	No	No	Yes
The setting of reimbursement prices when generic comes to market		40% of the net manufacturer shipping price of the patented product + official wholesaler margin + official pharmacy margin + value-added tax	Net manufacturer shipping price (set freely by the pharmaceutical company) + official wholesaler margin + official pharmacy margin + tax	Price set by the pharmaceutical company (with the price of the patented product as the upper limit)	Price negotiated between pharmaceutical company and insurer	50% of the price of the patented product (or 40% for internal drugs if more than 10 are added at the same time)
Revisions to reimbursement prices		Reviewed as appropriate	Review of reference prices (yearly)	Set based on the customer purchase price (every three months) so that the total pharmacy profit is £800 million	Price negotiated between pharmaceutical company and insurer	Set based on the customer purchase price (every two years)
Price brackets for generic reimbursement prices		One price bracket	Many price brackets	In principle, one price bracket + labeled generics	Many price brackets	Maximum of three price brackets (80% have one price bracket.)
Indicators of Market Penetration of Generics††						
Percentage of generics in total market	Volume base*	33% (2015)[1]	76% (2014)[1]	77% (2014)[1***]	79% (2014)[1]	34% (2015)[2]
	Value base	19% (2015)[1]	35% (2014)[1]	37% (2014)[1***]	18% (2014)[1]	12% (2015)[2]
Percentage of generics in off-patent market	Volume base*	78% (2015)[1**]	85% (2014)[1]	N/A	92% (2014)[1]	56% (2015)[2]
	Value base	70% (2015)[1**]	67% (2014)[1]	N/A	59% (2014)[1]	33% (2015)[2]
Percentage of INN prescriptions		15%[3]	N/A	84% (2014)[3]	89%[3]	31% (2016)[5****]
Percentage of non-substitutable prescriptions		22% (2012)[4]	14% (2010)[1]	No substitutions allowed	5%[3]	17% (2016)[5****]
(Reference) Public health system		National health insurance system	National health insurance system	National Health Service (tax supported)	Mainly public health care (Medicare and Medicaid[*****]) and private medical insurance	National health insurance system

†) Cells in the table are colored for issues considered problematic.
††) The period when data was collected is shown in parenthesis, if known.
*) For France, the base is number of boxes. For Germany and the United Kingdom, the base is number of

prescriptions.
**) For France, the percentage of generics in off-patent market excludes the hospital market.
***) For the United Kingdom, the percentage of generics in the total market refers to the percentage of all prescriptions for which the price of the generic was reimbursed.
****) Calculated on an item basis.
*****) Medicare is the federally administered medical insurance system for people 65 and up. Medicaid is the state-administered medical insurance system for low-income people.
1) Research report on drug usage (2016); Institute for Health Economics and Policy
2) Survey of drug prices in September of 2015, based on the overview of revisions to drug price standards (March 4, 2016); MHLW
3) Furnished documents, JPWA study meeting (September 2016); IMS UK
4) Report on adjustment of medical expenses based on generics (2013); National Federation of Health Insurance Societies
5) Report on the impact and implementation of policies to promote the use of generics (fiscal 2016 report); MHLW

6. Other Conditions Related to the Productivity of Medical Pharmaceuticals Distribution

This section summarizes various countries' approaches to bar code labeling and product returns as related to improving the overall handling productivity of pharmaceutical drugs, including generics.

A) Approach to Bar Code Labels Related to Product Information

The purposes of bar code labeling on medical pharmaceuticals include appropriate inventory management, the assurance of traceability, and the prevention of dispensing errors. In various countries, efforts have been made to strengthen regulations specifically to prevent the infiltration of counterfeit pharmaceutical drugs in recent years.

1) EU

Under current conditions, expiration dates and manufacturing numbers are displayed on the dispensing package unit, sales package unit, and original package unit.

In 2016, the EU decided on the specific content of the Falsified Medicines Directive (FMD) adopted in 2011, and mandated its implementation by February 9, 2019. Pharmaceutical companies are required to display a two-dimensional bar code (see Figure 5) that carries the product code, lot number, expiration date, and random number (including safety information for some products) on sales packages and to adopt package tampering prevention measures.

Figure 5: Example of a two-dimensional bar code

For traceability, wholesalers are not responsible for verification if they do not purchase products from original pharmaceutical companies. Pharmacies bear this responsibility. As a result, pharmaceuticals can be supplied safely at a low cost, without restricting supply chains in the EU region.

2) US

In the United States, pharmacy bottles are in widespread use, such that the dispensing package and sales package are often the same. Currently, the expiration date is displayed on the sales package, and the manufacturing number is not required to be shown.

However, the *Drug Supply Chain Security Act* (DSCSA) introduced in November 2013 required all pharmaceutical companies to affix a 2D bar code comprised of a product code, lot number, expiration date, and random number on the sales package. It requires that this be achieved within four years of the introduction of the act, by November 29, 2017.

Under the same law, data registration management is conducted on the transfer of property rights in conjunction

with the acceptance at the unit of sale, starting January 2015. Unlike the EU, pharmaceutical wholesalers must trace everything until the time a drug is dispensed to a patient. This has made it difficult to achieve technological shared understanding, agreements, and joint projects to occur between pharmaceutical companies and pharmaceutical wholesalers.

While it would not be efficient for the DSCSA to be applied to all products, it is extremely effective for cold-chain products, given the nature of the diseases they are used to treat.

3) Japan

Because bar code labels are effective means of product collection, sales discontinuation, and fulfilling important obligations with regard to safety measures, it has been recommended that the scope of the labels be expanded. In recent years, efforts aimed at promoting their further use have been deemed necessary in terms of preventing the infiltration of counterfeit drugs into the distribution process.

Regarding bar code labels, product codes must be on the dispensing package unit, sales package unit, and original package unit, while the expiration date and manufacturing number must be on the sales package unit and original package unit (it must also be on the dispensing package of certain biological products), with efforts being made to meet this requirement.

Japan does not yet have special regulations that govern traceability records.

B) Returned Products

Based on questionnaires on returned products to the on-site personnel at pharmaceutical wholesalers in the United States and Europe and to pharmaceutical companies in Japan, we learned that products can be returned, whether patented or generic in both the United States and Europe via several routes: from the medical institution/pharmacy to the pharmaceutical wholesaler, from the pharmaceutical wholesaler to the pharmaceutical companies, or from the medical institution/pharmacy to the pharmaceutical company. However, returns are handled differently depending on the size of the individual supplier. We also learned that, when accompanied by a system change (such as a change in the prescription form), the pharmacy and the pharmaceutical wholesaler or the pharmaceutical company coordinate their response, and when it comes to updating package leaflets, the sale of pharmaceuticals packaged before those updates is sometimes approved for a certain period.

In the United States, a survey was conducted regarding product returns among members of the Healthcare Distribution Alliance (HDA).[20] The following are excerpts from the 2015 survey.

- The 2015 survey showed that the total annual cost of product returns was USD 3.3 million, and that 93% of returned products were returned in salable condition. Reasons for the returns included inventory surplus (88.9%), damage (3.5%), and product expiration (2.2%).
- With regard to cold-stored products, the *Good Storage and Distribution Practices for Drug Products*

established strict regulations regarding temperature control. These regulations require that all refrigerators and freezers used by organizations throughout the distribution process, including manufacturers, pharmaceutical wholesalers, hospitals, and pharmacies, are equipped with temperature monitoring devices and alarm systems. Also, information regarding temperature control is disseminated at each stage where the product is stored in a warehouse, from the manufacturer to the wholesaler, from the wholesaler to the pharmacy, and from the pharmacy to the patient or customer. Cold-stored returned products will only be accepted under these strict conditions.

- There are few companies that accept returns of repackaged products (e.g., when single or multi drugs are combined into a package for use by senior citizens).
- The actual procedures for product returns are often handled by product return specialists, such as reverse distributors.

7. Discussion

We have raised questions on the issues related to the package varieties of Japanese pharmaceuticals in Section 3 and described the pricing systems, conditions related to secure supply, and distribution productivity in various countries in Sections 4, 5, and 6, respectively.

In summary, in the United Kingdom, there is considerable government intervention in generic pricing due to the country's tax-based public health care system, while in the United States, pharmaceutical product transactions are subject to free pricing. In both cases, there are obstacles to the manufacturing and pricing of generics due to the pursuit of productivity. In Germany, the volume of distribution operations in the pharmacy market are expanding due to discount contracts between sickness funds and pharmaceutical companies aimed at reducing pharmaceutical expenses. Distribution problems are being faced in every country.

There is no significant supply problem in France, where the use of generics is still on the rise. The French system may very well provide a model that Japan can implement for its generic drug policies. However, it is important to note that French drug price reforms are not based on market price.

The systems in each country are related to their own historical context and health care systems, including health services supply systems and health insurance systems. Therefore, the advantages and disadvantages of those systems must be viewed from a variety of perspectives. Based on this, the following can be described as the lessons that Japan should learn from other countries.

A) Lessons regarding the Distribution of Generics in Various Countries

1) Generics are not viewed as out of stock if substitute products are available.

In the United States and Europe, a drug shortage may not be a big issue even when a problem occurs in some part of the generic supply. Possible reasons are that: 1) substitutes are available, and 2) generics supply is more stable than patented products. This notion has also been confirmed by conversations with pharmaceutical wholesalers in Europe.

In France, a generic drug can be substituted at the discretion of the pharmacist. In the United Kingdom and the United States, they use the INN generics, which do not contain the name of the pharmaceutical company. If two or three companies supply drugs with the same ingredients, they can be dispensed at the pharmacy's discretion. There are no supply problems in these countries (the situation in Germany is discussed below).

The number of generic packaging types in Japan is rather substantial compared with other countries, as discussed in Section 3. From the perspective of improving distribution productivity, environmental adjustments need to be made to ensure that this perspective becomes a part of mainstream thinking even in Japan's pharmaceutical distribution, which has thus far placed significant emphasis on differences in pharmaceutical companies (or brands).

2) Reimbursement price setting is a framework that considers distribution expenses

If "generics can be substitutable at any time," this also means that there is a price competition and no limit on lowering the price decline. France and Germany have introduced frameworks that take into consideration the per-package wholesale margins and pharmacy margins for distribution expenses when they set the reimbursement prices for pharmaceutical drugs, including generics, upon market entry. In addition, reimbursement price revisions do not directly reflect the market prices, and lower limits on per-package wholesale margins are guaranteed even when the price deteriorates.

Under Scheme M (Scheme W for pharmaceutical wholesalers) in the United Kingdom, the Ministry of Health revises Category-M generic reimbursement prices based on the margins earned by pharmacies utilizing the weighted averages of the sales prices and sales volumes of generics reported by the pharmaceutical companies and pharmaceutical wholesalers. It can be said that some consideration of distribution continuity is being made in setting reimbursement prices.

3) Extracting packaging types by ingredient

Japan has many packaging types compared with other countries. This is due to the number of pharmaceutical companies but is also due to different dispensing methods at the pharmacy: prescriptions drugs are either boxed up in a patient pack (EU) or put in a bottle (U.S.). Also, packaging types for the same ingredients, the same dosage forms, and the same specifications are restricted.

A patient pack is highly effective in terms of pharmaceutical inventory management and safety assurance, and this includes the traceability and security of the expiration date. Dispensing time reductions can allow pharmacists to spend more time interacting with patients, which is a desirable outcome in terms of allowing pharmacists to demonstrate their professional capabilities. Even the *Report from the Committee Investigating a Vision for the Work Practices of Doctors and Nurses* (April 6, 2017) stipulates that "we need to verify the efficacy of box dispensing from the perspective of improving the efficiency of dispensing activities." On the other hand, Japanese dispensing methods offer advantages in terms of securing storage space at the pharmacy and offering carry-home convenience to patients who have many prescriptions. Although the efficacy of patient packs is recognized, this is not necessarily enough to motivate a switch to that format.

4) Reflecting the added value of generics on the reimbursement price

In the United Kingdom, some labeled generics reward a higher reimbursement price when they come with value-added features (such as sustained-release tablets) or with a device which the original patented product did not provide. In the future, generics will play a more-central role in promoting the health of people, and greater emphasis on both the cost of generics and their quality will be a favorable development in terms of national healthcare systems.

5) Strict standards for the return of refrigerated products

The return of pharmaceutical drugs not only lowers the productivity of distribution, but also results in product safety issues. As was discussed in Section 6, the *Good Storage and Distribution Practices for Drug Products* established strict regulations regarding temperature control in the United States. Great care must be taken to ensure that product returns are only accepted under very strict conditions.

B) Points of Concern in Generic Distribution in Various Countries

1) Excessively strict price controls can result in a supply shortage

As was mentioned in Section 5, narrowing down the number of manufacturers due to excessive price controls contributes to supply shortages in the hospital markets in the United States and Europe. Regarding generics manufacturing, cost competition due to price controls and restrictions on capital investments forces generic manufacturers not to adapt to increasingly strict regulations related to manufacturing, such as GMP standards, not to manufacture generics, and to withdraw from the market. Such a case has been observed in markets where the tender system is employed, such as the United Kingdom and the United States remarkably, and somewhat in Germany.

With regard to cost competition among manufacturers, the creation of a single reimbursement price in the pharmacy market is believed to have the same effect as the tender system. Among the four countries examined in Section 4, generic reimbursement prices at pharmacies were the same in the United Kingdom and France. Generics in the pharmacy market in the United Kingdom stay within one price bracket that reflects actual market prices each quarter. This causes a situation in which the purchase prices for some products exceed the reimbursement price. When this situation occurs, the government raises the reimbursement price. Generics in France also fall within one price bracket, but price setting is controlled by the government so prices do not directly reflect the actual market prices. As a result, there are no serious occurrences of drug shortage.

It is important to learn the lesson from overseas examples, which show that excessively strict price controls invites unbridled cost competition and this is a factor in supply shortages.

2) Formularies at the insurer level invite pharmaceutical cost decreases, as well as decreases in productivity

Pharmacists have the ability to dispense substitute products at their own discretion in Germany, as in France. The German pharmacists must dispense the product whenever a substitute drug is available from the eligible products that are in the discount contract with the sickness fund. Section 3 confirmed the large number of packaging types in Germany, and this is possibly related to the discount contracts between sickness funds and pharmaceutical companies. As a result, pharmaceutical prices and co-payments have been reduced, but this has clearly caused an increase in the line-up of generics at pharmacies and an increase in the operation of pharmacies and pharmaceutical wholesalers.

8. Proposals

There has been rapid progress in the promotion of the use of generics in Japan in a short period of time. First, quantitative targets were set, followed by government-led incentives in the form of medical treatment fees and a concerted supply effort on the part of pharmaceutical companies. A focus, however, has been placed solely on achieving the quantitative targets, which has resulted in delays in developing distribution-related systems. Increasing productivity in generics distribution and handling has become a major issue in distribution.

In this report, however, we have been able to confirm that the excessive pursuit of productivity can cause obstacles to supply stability from cases outside Japan. In other words, stable supply and increased productivity are two sides of a coin, and policies that can balance the two competing needs are advisable.

We recommend that Japan implement the following five policy initiatives to enhance generics productivity and achieve supply stability.

1) Initiatives to Achieve Supply Stability

Mandate a minimum level of generics supply

Although there are a large number of packaging types in Japan, reducing the types handled at pharmacies would allow higher productivity in distribution as a whole. When it comes to the basic data for extracting packaging types, information on quality is currently being expanded in the "Blue Book" (quality data sheet), but information related to supply is sorely lacking. It is also clear that stockouts are occurring in overseas hospital markets due to the concentration of pharmaceutical companies. To ensure supply stability, it is necessary to have multiple pharmaceutical companies supply drugs in volumes above a certain level for each packaging type.

The current *Roadmap for the Further Promotion of Generics Use* (April 2013) presents an initiative for generic manufacturers to submit their plans for procuring active pharmaceutical ingredients and their supply capacity. As a future national initiative, one option to promote generics is to consider the details of the aforementioned plan when companies apply for drug price listing, and to only approve companies for the drug price list that are deemed to have supply capacity above a certain level. It is also necessary to consider setting supply volume standards for drugs that are already listed in the drug price list.

2) Initiative to Reduce Social Costs, Including Streamlining the Work of Dispensing Prescriptions

Laying the groundwork for widespread use of patient packs

As discussed in the Discussion section, the utility of patient packs is already recognized in Japan. It is essential to advance initiatives to use these products, even in a limited field, in terms of enhancing a pharmacist's interaction with patients. Pharmacists first need to gain a better understanding of the convenience of patient packs for patients and their ability to increase patient satisfaction.

In the mid-to-long term, examining narrowing down the number of packaging types of internal generics, for

example extracting packaging to three types including patient packs (14-day and 28-day) and large package of loose tablets (capsules), could be considered. Large packages of loose units are a solution for repackaging and the handling of cases where patient packs are not suitable.

In addition, several measures should be considered, including policies; 1) to match the prescription period and the contents volume of patient pack, 2) to adjust prescription if the prescription period and the contents volume of patient pack are not matched, 3) to prepare package leaflets for patients, 4) to set drug price specific to the packaging type, and 5) to revise prescription dispensing fees and technical fees for health insurance pharmacies. A multi-faceted approach is required, with integrated efforts on the part of the government, pharmaceutical companies, and health care providers.

3) Efforts to Achieve Distribution Sustainability

Reflecting appropriate distribution costs in reimbursement prices

In setting drug prices in Japan, the distribution costs of medical pharmaceuticals are taken into consideration only in the cost-accounting system for new drugs. Generic prices are set at 50% or 40% of the patent-expired product, but distribution costs are not revised. As the actual market price subsequently falls, these costs will be endlessly constrained.

The *Proposal regarding the Improvement of Commercial Transaction Practices of Ethical Drugs* issued by the Council for the Improvement of Commercial Transaction Practice of Ethical Drugs on September 1, 2015 states that there is a need to consider a system that is able to demonstrate ongoing distribution functionality while ensuring appropriate profits and covering the distribution costs for each individual drug. September 2020 was set as the target for reaching 80% generics use on a volume basis. Considering that 80% of the patent-expired market represents approximately 50% of the entire market, efforts must be made to quickly introduce a mechanism in the drug pricing system to appropriately reflect distribution costs in generic pricing. One possibility, for example, is to take into account distribution costs by setting an adjustment range corresponding to drug price levels.

Outside Japan, some countries have introduced a mechanism of official margins. Pharmacy management is challenging, however, and in the actual markets a portion of the wholesale margin flows to pharmacies, so introducing an official margin would not be a good solution for ensuring that distribution costs are covered. However, it must be recognized that setting reimbursement prices that directly reflect only the prevailing market prices runs counter to distribution sustainability.

4) Efforts to Facilitate Dispensing Changes

Greater patient education on generic quality

One feature of the Japanese system is that patient consent is required when making a dispensing change. To improve the productivity of generics going forward and to maximize the advantages of the drug substitution, it is necessary to alleviate the distrust of patients about not only substituting generics for patent-expired products, but

also about substituting generics for generics. Ongoing education for patients is needed to ensure they understand that, regardless of the pharmaceutical company, approved generics have the same efficacy as patent-expired products.

5) Efforts to Optimize Drug Distribution Management

Strict supply chain structures

To realize the viability of drug traceability, a Japanese version of the PIC/S GDP guidance documentation (see Footnote 1) should be studied. At the same time, mechanisms must be incorporated in the supply chain system to ensure its tight control. In light of recent cases of counterfeit drugs being distributed even in Japan, the system design must incorporate a framework for international cooperation that includes the progress made outside Japan and not just the domestic situation. For example, it is important to coordinate and conduct research with actors in the drug supply chain in Europe and the United States through participation in the IPDC (see Footnote 2) and other organizations.

We hope that this report will serve as a trigger for medical pharmaceutical distributors to have lively discussion on how to ensure stable supply and to improve productivity after the goal of achieving 80% generic use on a quantitative basis is achieved.

Note: 1 PIC/S GDP Guidelines: Guidelines on appropriate drug distribution standards issued by the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (as of 2017, 46 countries are members. Japan became a member in July 2014)

Note 2: IPDC: International Pharmaceutical Distribution Conference

Explanation 1: Comparison of Reference Price Systems in France and Germany

Both systems were instituted for the purposes of promoting generics use and controlling pharmaceutical expenses. Although both systems have patients bear the cost difference when selecting a drug that exceeds the upper limit of the reimbursement amount, they differ in many other ways. These differences have been summarized in the following table.

Appended Table 1. Comparison of Reference Price Systems in France and Germany

	France	Germany
Grouping requirement	If, after the patent expires, the proportion of generics on a volume basis does not reach 55% in one year, 60% in 18 months, 65% in two years, and 80% in three years, the drug price transitions to TFR (Tarifs Forfaitaires de Responsabilite, or reference pricing)	Group similar drugs from the standpoint of their active ingredients, mechanism of action, medicinal effect, etc.
Drugs making up groups	Patent-expired products and their generics with identical ingredients, specifications, and packaging	Patented products, patent-expired products, and their generics whose ingredients are: Class 1: Identical Class 2: Pharmacologically and therapeutically equivalent Class 3: Therapeutically equivalent (drug combinations, etc.) and when the specifications and packaging are the same.
No. of groups	407 groups (2017)	428 groups (2014)
Proportion of products transitioning to a group	Approx. 18% on a value basis	43% on a value basis, 73% on a volume basis
How the reimbursement upper limit is decided	(TFR price) Average price of the generics	(Reference price) Set in the range that does not exceed one-third of the price difference of the most-expensive drug and the least-expensive drugs in the group
Cost difference when selecting a drug that exceeds the reimbursement upper limit	Borne by patient	Borne by patient
Revision of reimbursement upper limit	As appropriate	Once/year in principle
Retail pharmacy price trends for grouped drugs	(Fig. 3-1: See application of the reference price system) Drugs that have transitioned to the TFR can have open prices, but in many cases the retail pharmacy price for both the patent-expired product and the generic are packaged at the level of the reimbursement upper limit (with the exception of some patent-expired products whose price does not drop)	(See Fig. 4) Retail pharmacy prices are generally not the same. Drug prices may be lower than reference prices due to such factors as exemptions on patient-borne expenses for products with a pharmacy retail price 30% or more less than the reference price, and discount contracts concluded between sickness funds and pharmaceutical companies. In some cases, prices are the same.
Year introduced	2003	1989

Source: Institute for Health Economics and Policy

Explanation 2: UK's Pharmaceutical Price Regulation Scheme (PPRS)

The following is an overview of the UK drug price system that forms the basis of its reimbursement pricing.

○ Scheme M[21]

The scheme was established in April 2005 for setting reimbursement prices for generics that have received approval under INN. This scheme created the Category-M drug category of the Drug Tariff (see below).

Under this scheme, generic pharmaceutical companies submit information each quarter to the Department of Health, including their revenue, by packaging type, discounts and rebates, sales volumes, and an updated list of transaction prices. When they enter the market, pharmaceutical companies can freely set the price of a drug without having to gain approval as long as the price is lower than the price of the patented drug. That price becomes the reimbursement price. After the drug is on the market, the company must submit the aforementioned data monthly for the first one to two quarters.

Pharmaceutical wholesalers also participate in Scheme M and in addition to the aforementioned data, submit data on payments to pharmaceutical companies by packaging type and purchase volumes.

The Department of Health uses this data to calculate the weighted average of net manufacturer shipping prices, decides the reimbursement prices of Category M drugs so that pharmacy profits reach £800 million (as of May 2017), and publishes the amended Drug Tariff each quarter.

In principle, prices are left to market mechanisms, but the Department of Health intervenes if market competition is deemed to be insufficiently effective. When this happens, pharmaceutical companies must submit data including direct and indirect manufacturing and supply expenses, reasons why cost increases are unavoidable, the reasonableness of the gross operating profit of other products sold by the company, sales during the previous year, and estimated sales for the current and following year.

○ Drug Tariff[3]

Part VIII of the Drug Tariff (issued monthly) contains a list of the generics of pharmaceuticals prescribed on an outpatient basis and the reimbursement price to pharmacies. Pharmaceuticals are divided into the categories A, B, C, D, and M. The majority are classified as categories A, C, and M.

Patented drugs are classified as Category C, and their labeled names are included. Prices can be freely set by the drug manufacturer based on the Pharmaceutical Price Regulation Scheme (PPRS), which contains the price-setting rules for patented drugs. This is set as the reimbursement price and is almost never changed.

Generics are applicable to categories A or M. The majority are classified as Category M. Prices are decided based on Scheme M (described above) and revised every three months.

In addition, Scheme M is a system for setting reimbursement prices for INN generics; labeled generics are not included here. As with patented drugs, prices for labeled generics are decided under the PPRS. They are included in categories C or A, not Category M. The labeled name and price are not necessarily listed in the Drug Tariff. Prices are almost never changed.

In the *Monthly Index of Medical Specialties* (MIMS, issued on the first of every month), a price list published by a private company, all reimbursement prices for patented products, patent-expired products, INN generics, and labeled generics are listed together with the product name. Examples of Drug Tariff and MIMS prices are shown in Appended Table 2.

Appended Table 2. Drug Tariff and MIMS Price Comparison

Drug Tariff: Reimbursement price for generic name prescriptions

MIMS: Reimbursement price when prescription uses the product name

	Description and Price in the Drug Tariff					Description and Price in MIMS		
Patented product (Sectral)	Drug	Quantity	Basic Price	Category				
	Acebutolol 100mg capsules	84	1497	C	Sectral	Sectral Caplules	100mg, 84=	£ 14.97.
	Acebutolol 200mg capsules	56	1918	C	Sectral		200mg, 56=	£ 19.18.
	Acebutolol 400mg tablets	28	1862	C	Sectral	Sectral	400mg, 28=	£ 18.62.
Patent-expired product (Amias)	Drug	Quantity	Basic Price	Category				
	Candesartan 2mg tablets	7	192	△M		Amias	2mg, 7=	£ 3.58.
	Candesartan 4mg tablets	7	66	▽M			4mg, 7=	£ 9.78.
	Candesartan 8mg tablets	28	98	▽M			8mg, 28=	£ 9.89.
	Candesartan 16mg tablets	28	115	▽M			16mg, 28=	£ 12.72.
	Candesartan 32mg tablets	28	159	▽M			32mg, 28=	£ 16.13.
						Candesartan	2mg, 7=	£ 1.92.
							4mg, 7=	66p.
							8mg, 28=	98p.
							16mg, 28=	£ 1.15.
							32mg, 28=	£ 1.59.

The necessary items were extracted from the both lists, and the order of products rearranged for simplicity.

The basec price unit in Drug Tariff is £. Labeled names are included during the patent period.

△ in the Category shows increase and ▽ shows decrease from the previous month.

(Source: Drug Tariff January 2007, MIMS April 2017)

Explanation 3: Rules Governing Substitutions

○ France[6]

When a patent-expired product or a generic is prescribed, and unless the prescribing physician specifies their intention to not allow substitutions and the reason for this on the prescription, the pharmacist may dispense a substitute drug within the same generic drug group. In this case, the pharmacist must write the name of the drug actually given to the patient on the prescription.

The National Agency for the Safety of Medicines and Health Products (ANSM) creates the generic drug groups at the time of approval of generics. This is the legal basis of dispensing substitute drugs and guarantees for doctors, pharmacists, and patients that generics are exactly the same as the patented product.

○ Germany

Rules obligate pharmacists to make generics substitutions.

a) *Substitute Drug Dispensing Law* (July 2002) and *Substitute Drug Dispensing Rules* (May 2004)[9]

Unless dispensing a substitute drug is explicitly prohibited on the prescription, pharmacists must decide to dispense prescriptions with cheaper drugs as long as requirements for biological equivalence are met (some rules apply). The prescribing physician does not need to be notified or consulted at this time.

b) Discount contracts through bidding by sickness funds (2007)[8]

Sickness funds select pharmaceutical companies (companies within the EU are eligible) to supply drugs at economical prices for a set period (maximum of two years) through a bidding process, and are able to conclude a discount contract with that drug manufacturer. When it is possible to substitute an eligible generic in the discount contract, pharmacists must dispense that product unless the physician has written on the prescription that drug substitutions are not permitted.

○ UK[22]

In the United Kingdom, INN prescriptions are standard. When patented products, patent-expired products, and labeled generics are prescribed, the prescription must be dispensed with that drug.

Pharmacists can dispense INN prescriptions with either the patent-expired product or the generic, but the

reimbursement price is the price listed in the Drug Tariff, which is the generic price. For INN prescriptions, there is no requirement to report to the physician which generic was dispensed.

○ US[23]

The regulations vary by state, but drug substitutions are permitted in all 50 states and are required in 12 states.

○ Japan[24]

In Japan, drug substitutions are referred to as "dispensing changes." One feature of the Japanese system is the ability to change a drug, within the scope of dispensing changes, to one with a different content specification or a different dosage form. Another feature is that patients must be given an explanation of the dispensing change. As a rule, information on the dispensing change should be provided to the prescriber.

Explanation 4: Dispensing Method and Pharmaceutical Packaging Forms in Pharmacies

Variations in packaging types are closely related to the country's method of dispensing prescriptions. Use of patient packs is widespread outside Japan, and prescriptions are typically dispensed by handing a box or bottle to the patient.

1) EU

Pharmaceuticals are not taken out of the outer box, and the pharmacist gives the patient a box corresponding to the quantity written on the prescription. This method of dispensing prescriptions is called "box dispensing." In the United Kingdom, drug quantities per box are five or seven days for an acute period, and 28 or 30 days for a chronic period.[25] In Germany, packaged box forms are regulated by the *Box Packaging Size Law* and are divided into N1 (about 10 days for patients in an acute period), N2 (average size of about 30 days), and N3 (long-term prescriptions of about 100 days).[26]

2) US

Prescriptions are dispensed in the unit of a bottle filled with loose tablets (loose capsules) corresponding to the quantity written on the prescription. Bottles often contain 30 tablets, and pharmaceuticals in high demand are divided into smaller bottles from a bulk bottle containing 1,000 tablets or similar.[27]

3) Japan

When pharmaceuticals are delivered, the outer box is opened, and the drugs are stored in a medicine cabinet. The pharmacist inserts the medicine into medicine packets corresponding to the prescribed dose written on the prescription and dispenses it to the patient. Many packaging types with slight variations are prepared according to the conditions at the customer. Packaging designed for pharmacies includes small PTP packages and loose packaging for dispensing drugs in a single container, and packaging designed for hospitals includes large packages. Generics are often also prepared in packaging that conforms to the patented product. This constrains inventory space at pharmaceutical wholesalers and is one factor behind cost increases related to the drug product lineups.

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